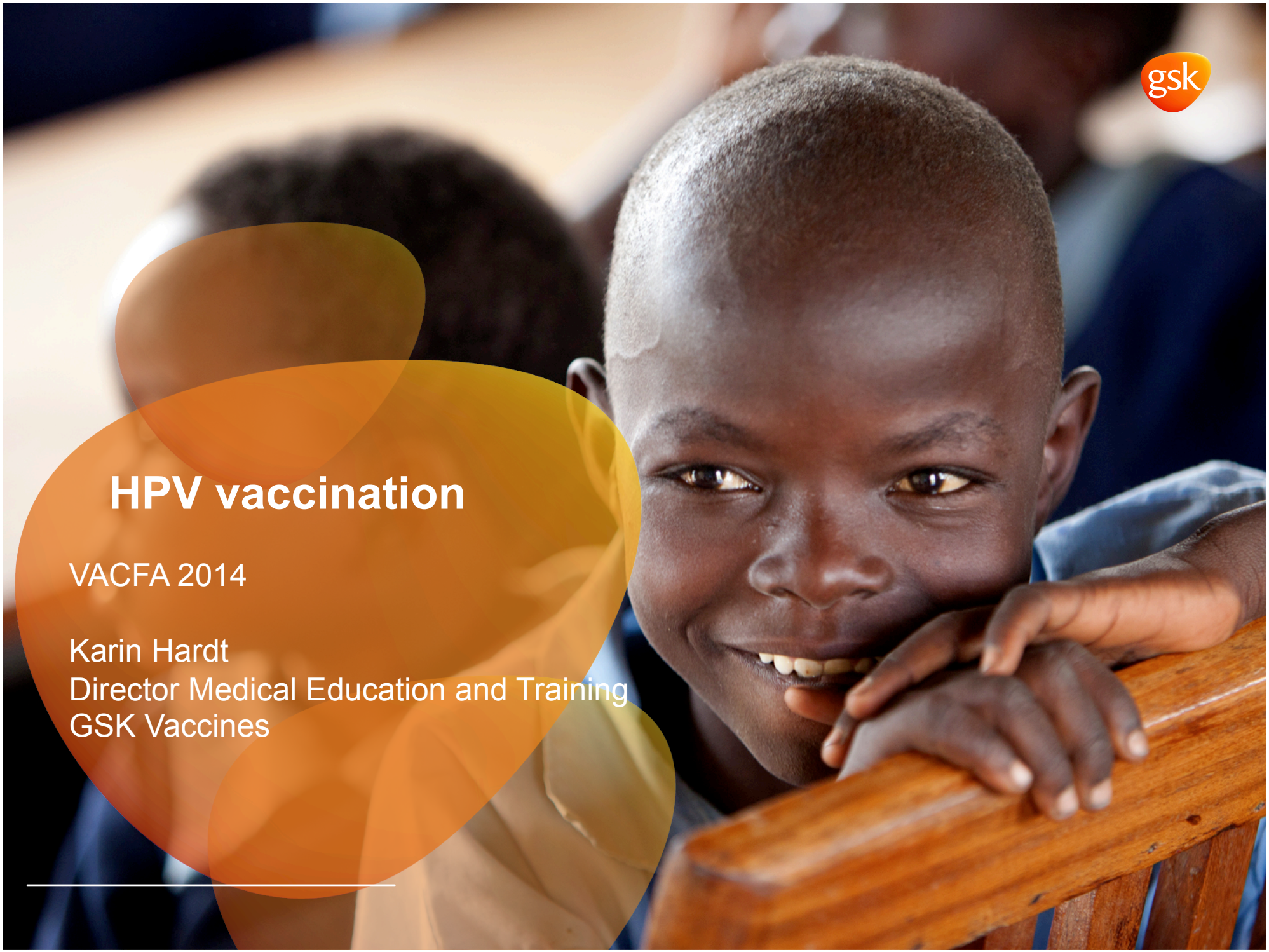


HPV vaccination

VACFA 2014

Karin Hardt
Director Medical Education and Training
GSK Vaccines

Disclosure of interests

- Karin Hardt is an employee of GSK Vaccines in Belgium, in charge of Vaccine Medical education and training

Outline

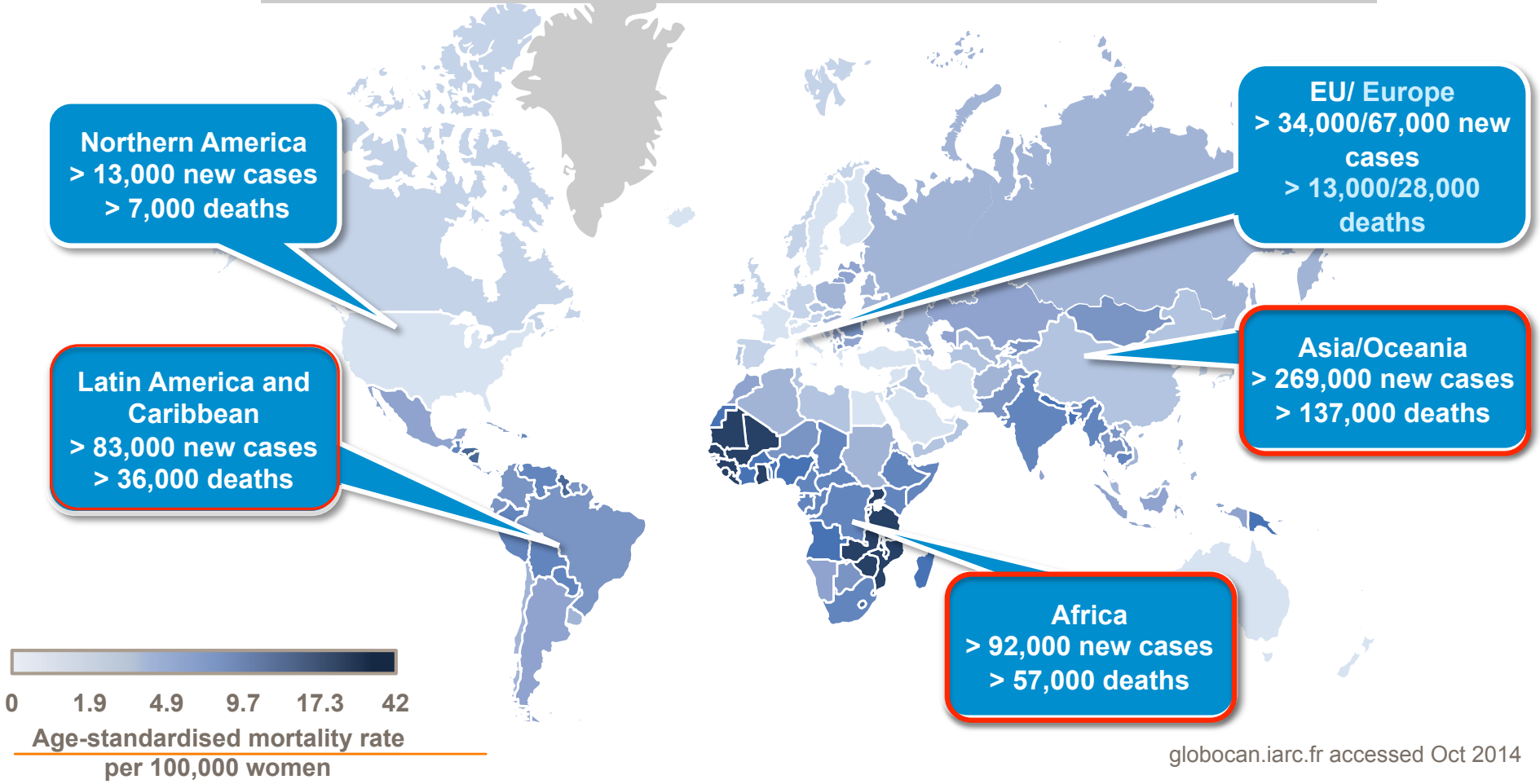
- Cervical cancer and Human Papillomavirus
  - Disease burden of cervical cancer
  - Description of the pathogen
  - Role of high-risk HPV types to cause cervical and other cancers
- HPV vaccines
  - Characteristics of current HPV vaccines
  - Efficacy, immunogenicity, cross-protection and duration of protection
  - Safety of HPV vaccines
- Public Health Considerations

Cervical cancer and Human Papillomavirus

Cervical cancer burden – World Wide

Every minute a woman is diagnosed with cervical cancer.[1]

Every 2 minutes a woman dies of cervical cancer.[1]



globocan.iarc.fr accessed Oct 2014

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F (2013).
GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer.).

Ranking of Cervical cancer in the world

	Female population 15+ years (in millions)	Nr of new cases annually	Nr of deaths annually	Ranking of Cervical cancer in women	
				aged 15 to 44 years	All women
World	2645.08	527,624	265653	2nd	4th
Africa	331.40	99,038	60098	2nd	2nd
Asia	1591.28	284,823	144434	2nd	3rd
Europe	328.65	58,373	24385	2nd	6th
Oceania	14.73	2,195	1063	3nd	8nd
Americas	379.02	83,195	35673	2nd	4th

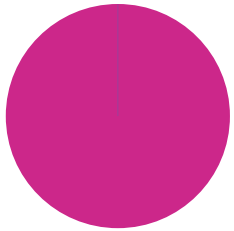
http://www.hpvcentre.net/statistics/reports/XWX.pdf
SUMMARY REPORT 2014

Estimates of global burden of HPV associated cancer

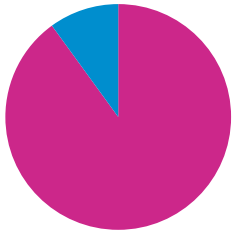
High-risk HPV associated

Other cause

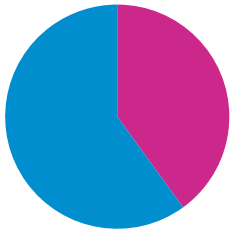
Cervical Cancer



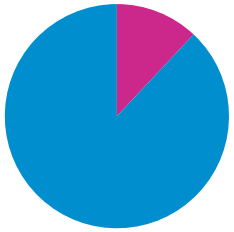
Anal Cancer



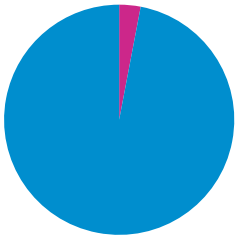
Vulva, Vagina, Penile Cancers



Oropharynx Cancer



Mouth Cancer

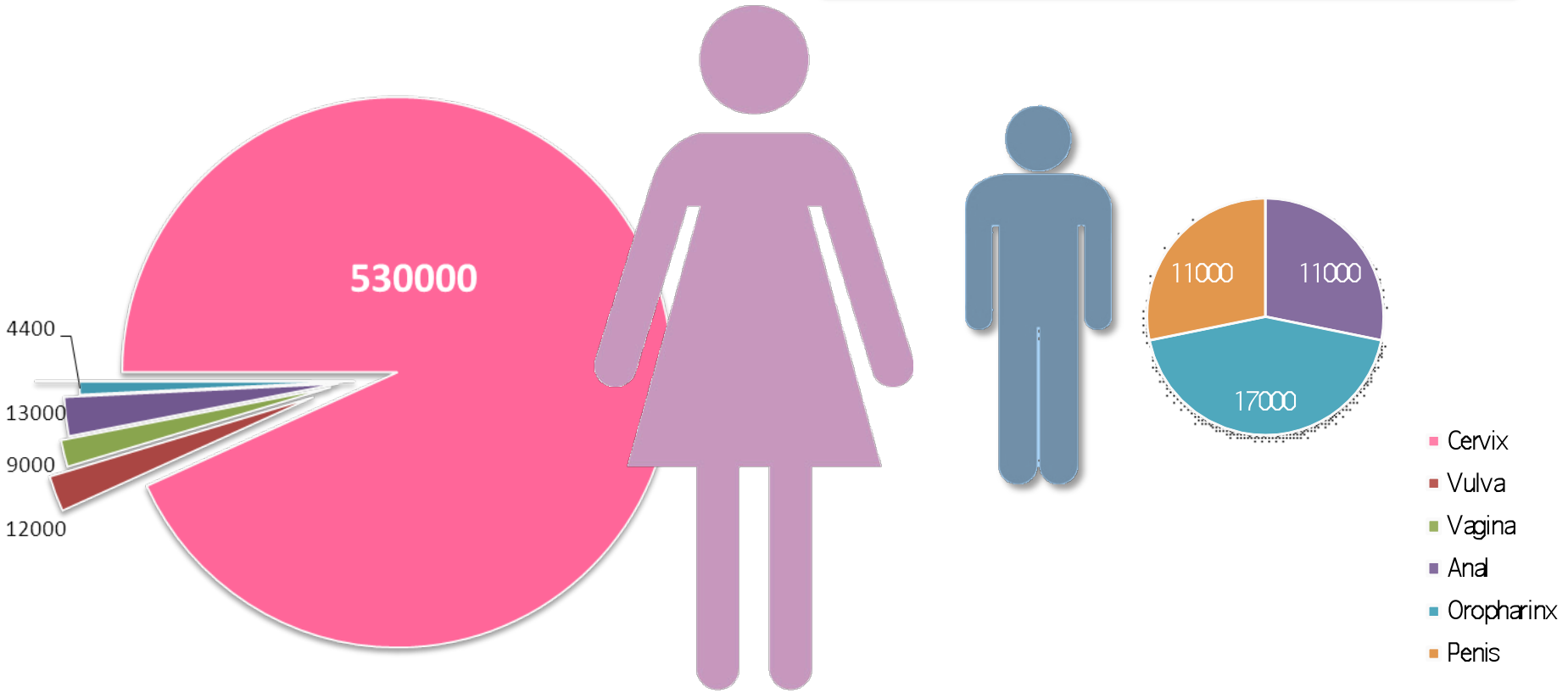


Reference: Cutts *et al*., 2007, Bulletin of WHO; Harper & Williams, Discovery Medicine 2010

Introduction: Global burden of HPV-related cancers - Highest burden in cervical cancer

HPV-related cancer in women
568,400 cases WW/year

HPV-related cancer in men
39,000 cases WW/year

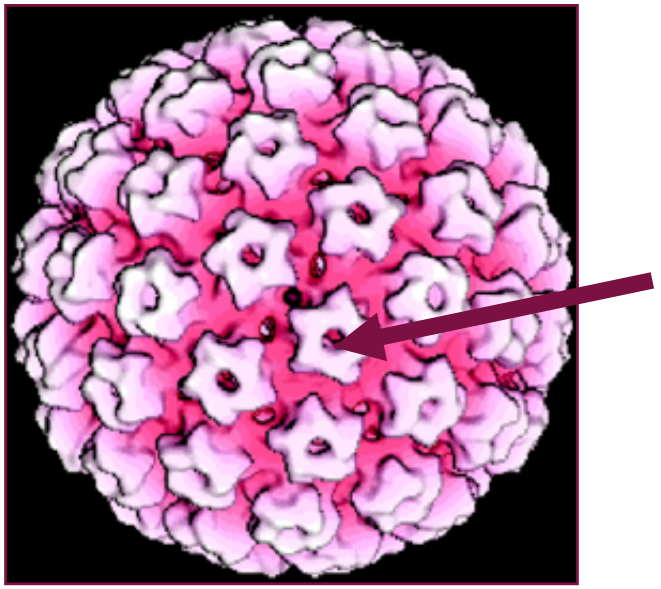


90% of HPV cancers in women are cervical cancers

Adapted from de Martel C et al. Lancet. 2012;13:607-615

The Human Papillomavirus

- Small, double-stranded DNA virus that infect the epithelium.
- Viral capsid is composed of two proteins, L1 and L2.
- More than 100 HPV types identified.
- Most HPV types infect cutaneous epithelium.
- 40 types infect the mucosal epithelium.



Reference: Chen XS, Mol Cell. 2000; 5(3):557-67; with permission from Elsevier.

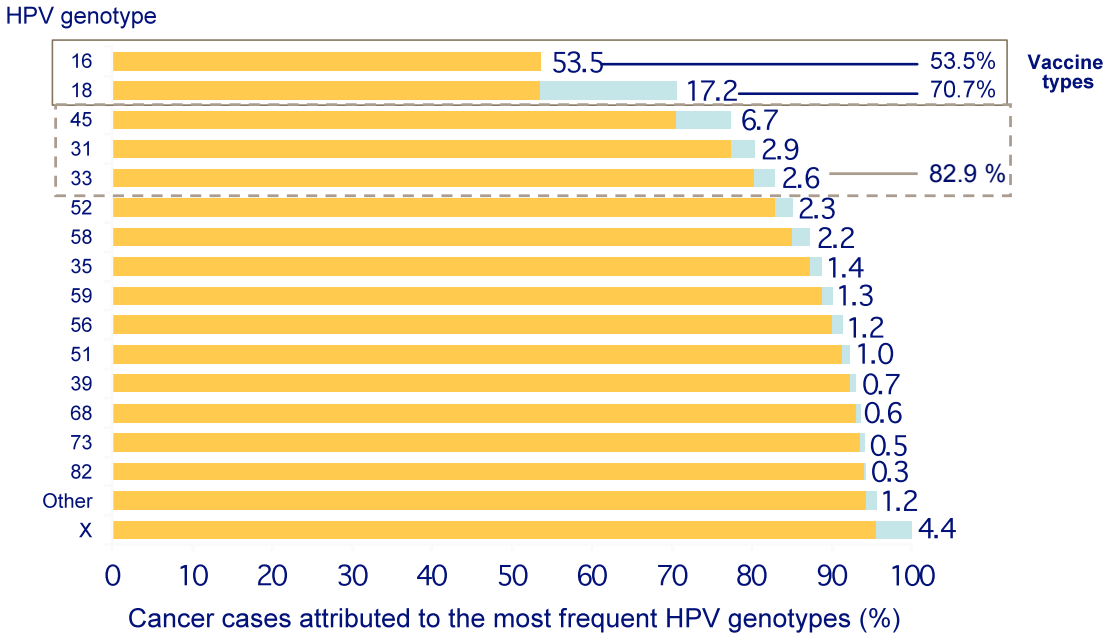
HPV infection and cervical cancer

- Cervical Cancer is due to high-risk HPV
- Up to 80% of women will acquire an HPV infection in their lifetime and 50% of these infections will be with a high-risk HPV type
- HPV infection often acquired within 5 years after sexual debut
- Most infections are asymptomatic and are cleared within 2 years
- Only a fraction of women (persistent) infected with high-risk HPV will develop cervical cancer, most infections resolve spontaneously

Bosch FX, de Sanjose S. *J Natl Cancer Inst Monogr* 2003; 3-13
Brown DR, et al *J Infect Dis* 2005; 191: 182-192
Baseman JG, Koutsky LA. *J Clin Virol* 2005:32 Supp I: S16-24

HPV type distribution in cervical cancer

- Fifteen oncogenic HPV types can cause pre-cancerous lesions & cervical cancer
- The 5 most frequent HPV types associated with cervical cancer globally are types 16, 18, 45, 31, and 33, accounting for about 83% of cervical cancer globally.
- HPV 16/18 are responsible for about 52% of high grade lesions, 70% cervical cancer worldwide
- Most low-risk types have not been demonstrated to be causing cervical cancers



Adapted from Munoz N et al. *Int J Cancer* 2004;111:278–85.

1. Bosch FX, *et al. Vaccine* 2008: 26S;K1-K16
2. Garnett G *et al. Vaccine* 2006;26(3):S178-86
3. Goldie SJ *et al. J Natl Cancer Inst* 2004;96:604-15.

HPV Types contributing to the Cervical Cancer Burden in South Africa.

Table 4. Distribution of HPV types (% [95% confidence interval]) among women with histologically confirmed invasive cervical cancer infected with a single HPV type

HPV type[1]	Ghana (N^2 = 121)	Nigeria (N^2 = 145)	South Africa (N^2 = 181)	Total (N^2 = 447)
HPV16	55.4 [46.1, 64.4]	52.4 [44.0, 60.8]	47.5 [40.1, 55.1]	51.2 [46.5, 56.0]
HPV18	19.0 [12.4, 27.1]	14.5 [9.2, 21.3]	18.2 [12.9, 24.6]	17.2 [13.8, 21.1]
HPV35	6.6 [2.9, 12.6]	9.0 [4.9, 14.8]	9.9 [6.0, 15.3]	8.7 [6.3, 11.7]
HPV45	6.6 [2.9, 12.6]	7.6 [3.8, 13.2]	7.7 [4.3, 12.6]	7.4 [5.1, 10.2]
HPV33	3.3 [0.9, 8.2]	1.4 [0.2, 4.9]	6.6 [3.5, 11.3]	4.0 [2.4, 6.3]
HPV52	2.5 [0.5, 7.1]	2.8 [0.8, 6.9]	1.7 [0.3, 4.8]	2.2 [1.1, 4.1]
HPV51	1.7 [0.2, 5.8]	2.8 [0.8, 6.9]	1.1 [0.1, 3.9]	1.8 [0.8, 3.5]
HPV31	0.8 [0.0, 4.5]	2.1 [0.4, 5.9]	1.7 [0.3, 4.8]	1.6 [0.6, 3.2]
HPV68/73	0.8 [0.0, 4.5]	0.0 [0.0, 2.5]	2.8 [0.9, 6.3]	1.3 [0.5, 2.9]
HPV56	1.7 [0.2, 5.8]	0.7 [0.0, 3.8]	1.1 [0.1, 3.9]	1.1 [0.4, 2.6]
HPV59	0.0 [0.0, 3.0]	2.8 [0.8, 6.9]	0.6 [0.0, 3.0]	1.1 [0.4, 2.6]
HPV39	0.8 [0.0, 4.5]	1.4 [0.2, 4.9]	0.6 [0.0, 3.0]	0.9 [0.2, 2.3]
HPV58	0.8 [0.0, 4.5]	1.4 [0.2, 4.9]	0.0 [0.0, 2.0]	0.7 [0.1, 1.9]
HPV53	0.0 [0.0, 3.0]	0.7 [0.0, 3.8]	0.0 [0.0, 2.0]	0.2 [0.0, 1.2]
HPV66	0.0 [0.0, 3.0]	0.0 [0.0, 2.5]	0.6 [0.0, 3.0]	0.2 [0.0, 1.2]
HPV70	0.0 [0.0, 3.0]	0.7 [0.0, 3.8]	0.0 [0.0, 2.0]	0.2 [0.0, 1.2]

[1]In 11 HPV positive women, the HPV type could not be determined.
[2]N = total number of women infected with a single HPV type.

Denny et al. 2103, International Journal of Cancer,

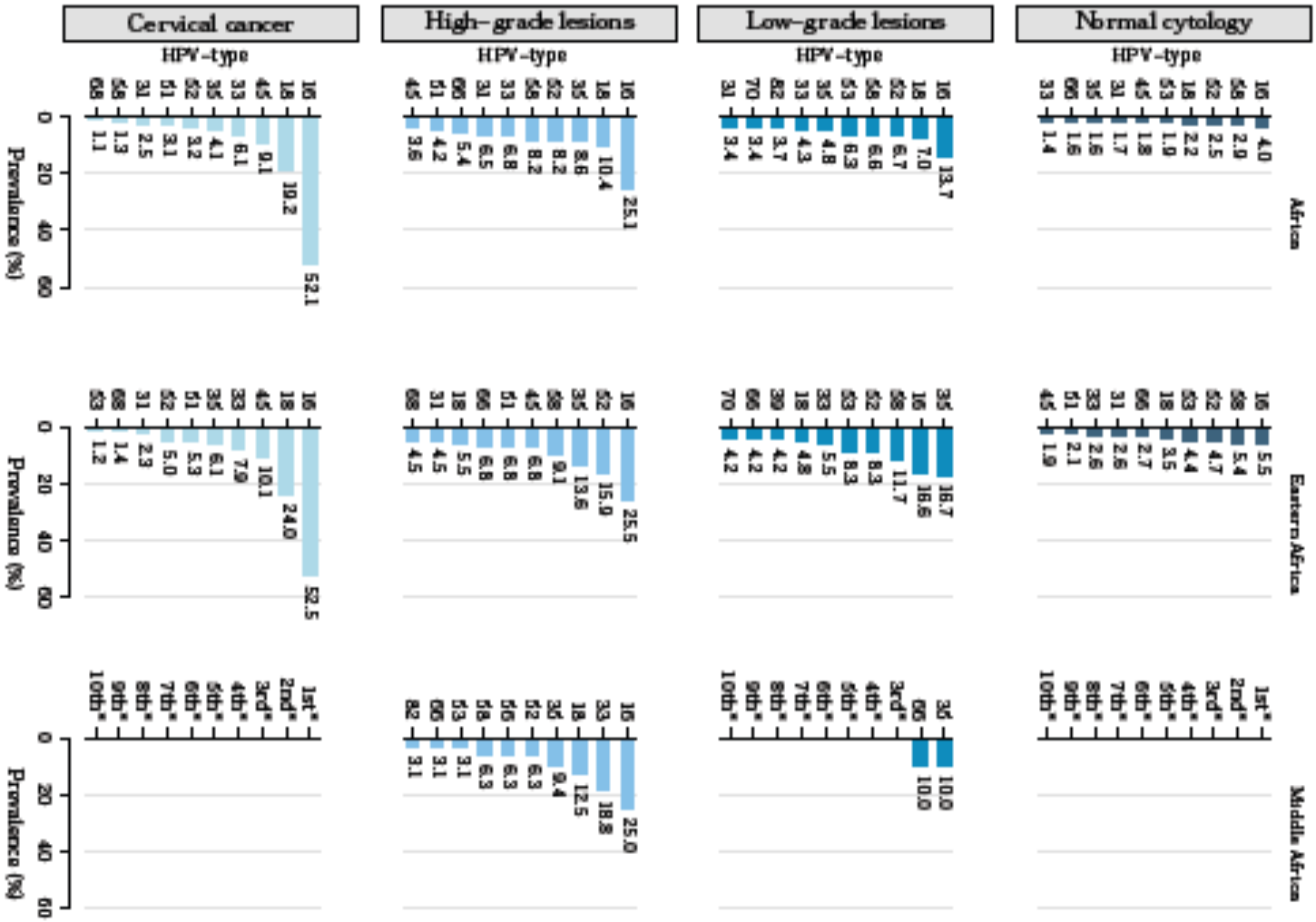
Key statistics in Africa and its regions

Population	Africa	Eastern Africa	Middle Africa	Northern Africa	Southern Africa	Western Africa
Women at risk for cervical cancer (Female population aged >=15 yrs) in millions	306.490	96.140	34.560	68.770	21.280	85.740
Burden of cervical cancer						
Annual number of new cervical cancer cases	99,038	45,707	11,540	5,813	8,652	8,652
Standardized incidence rates per 100,000 population in cervical cancer	27.6	42.7	30.6	6.6	31.5	31.5
Annual number of cervical cancer deaths	60,098	28,197	7,917	2,717	4,721	4,721
Standardized mortality rates per 100,000 population in cervical cancer	17.5	27.6	22.2	3.2	17.9	17.9
Burden of cervical HPV infection						
HPV prevalence (%) in the general population (women with normal cytology)	24.9	35.8	-	10.7	21.0	21.0
Prevalence (%) of HPV 16 and/or HPV 18 among women with:						
Normal cytology	6.2	9.0	-	5.1	3.6	3.6
Low-grade cervical lesions (LSIL/CIN-1)	20.7	21.4	0.0	18.5	21.1	21.1
High-grade cervical lesions (HSIL/ CIN-2 / CIN-3 / CIS)	35.5	31.0	37.5	40.0	30.0	30.0
Cervical cancer	71.3	76.5	-	78.4	62.8	62.8

LSIL, low-grade intraepithelial lesions; HSIL, high-grade intraepithelial lesions; CIN-2/3, cervical intraepithelial neoplasia grade 2 or 3; CIS, carcinoma in-situ.

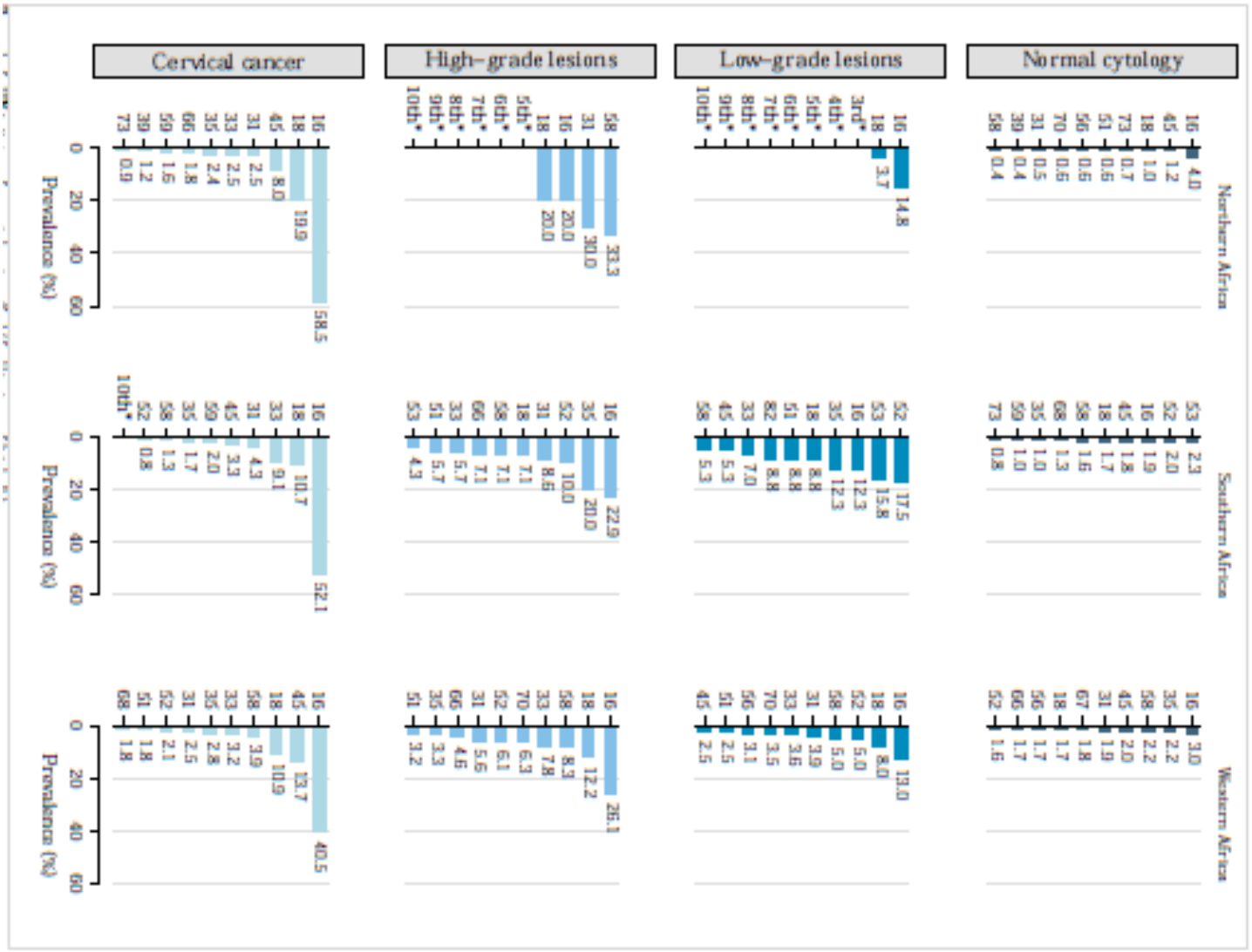
http://www.hpvcentre.net/statistics/reports/XFX.-pdf accessed Oct 2014

10 most frequest HPV oncogenic types among women w/wo cervial lesions in regions of Africa



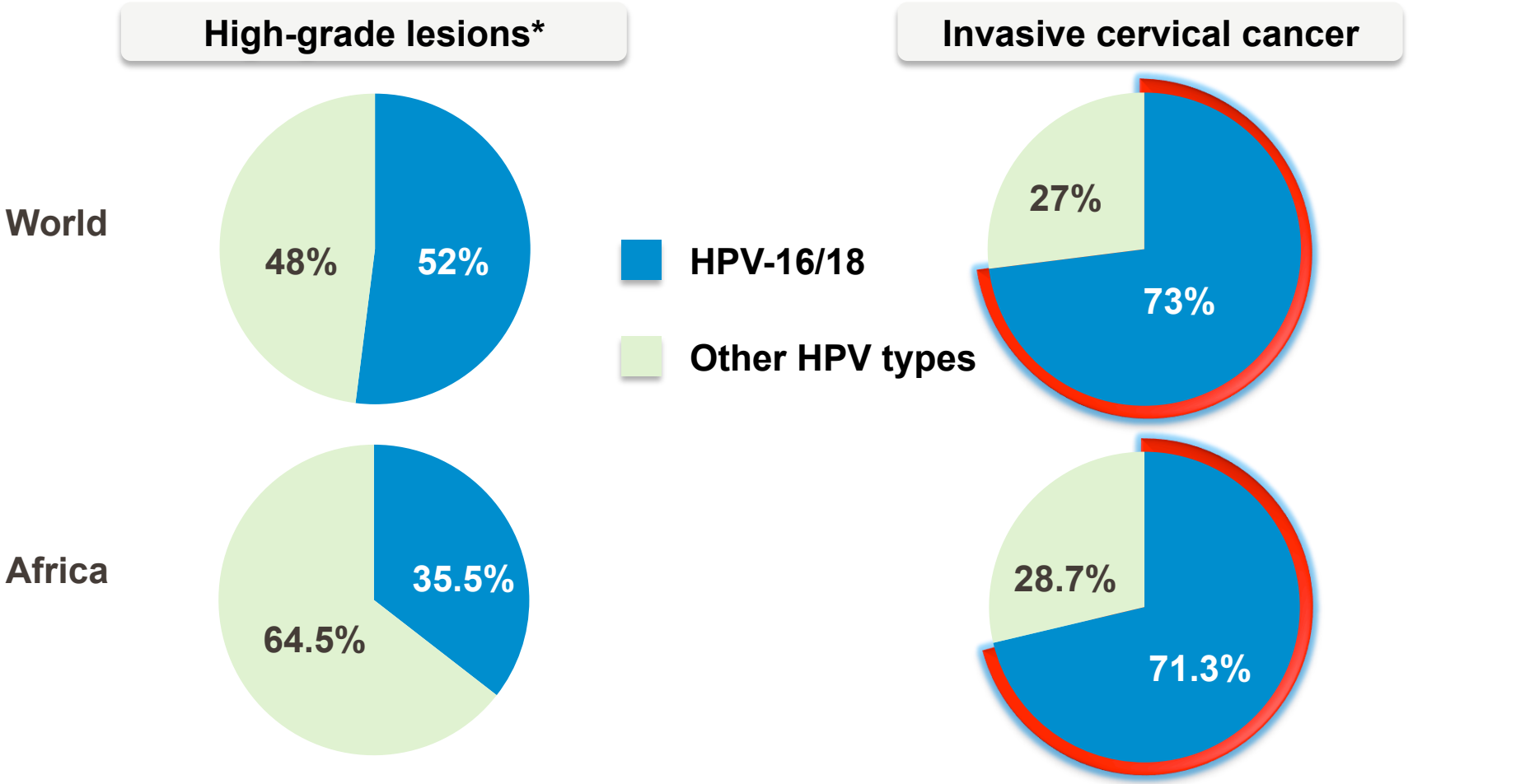
http://www.hpvcentre.net/statistics/reports/XFX.-pdf accessed Oct 2014

10 most frequest HPV oncogenic types among women w/wo cervial lesions in regions of Africa



http://www.hpvcentre.net/statistics/reports/XFX.-pdf accessed Oct 2014

Most frequent HPV types in high-grade lesions and invasive cervical cancer

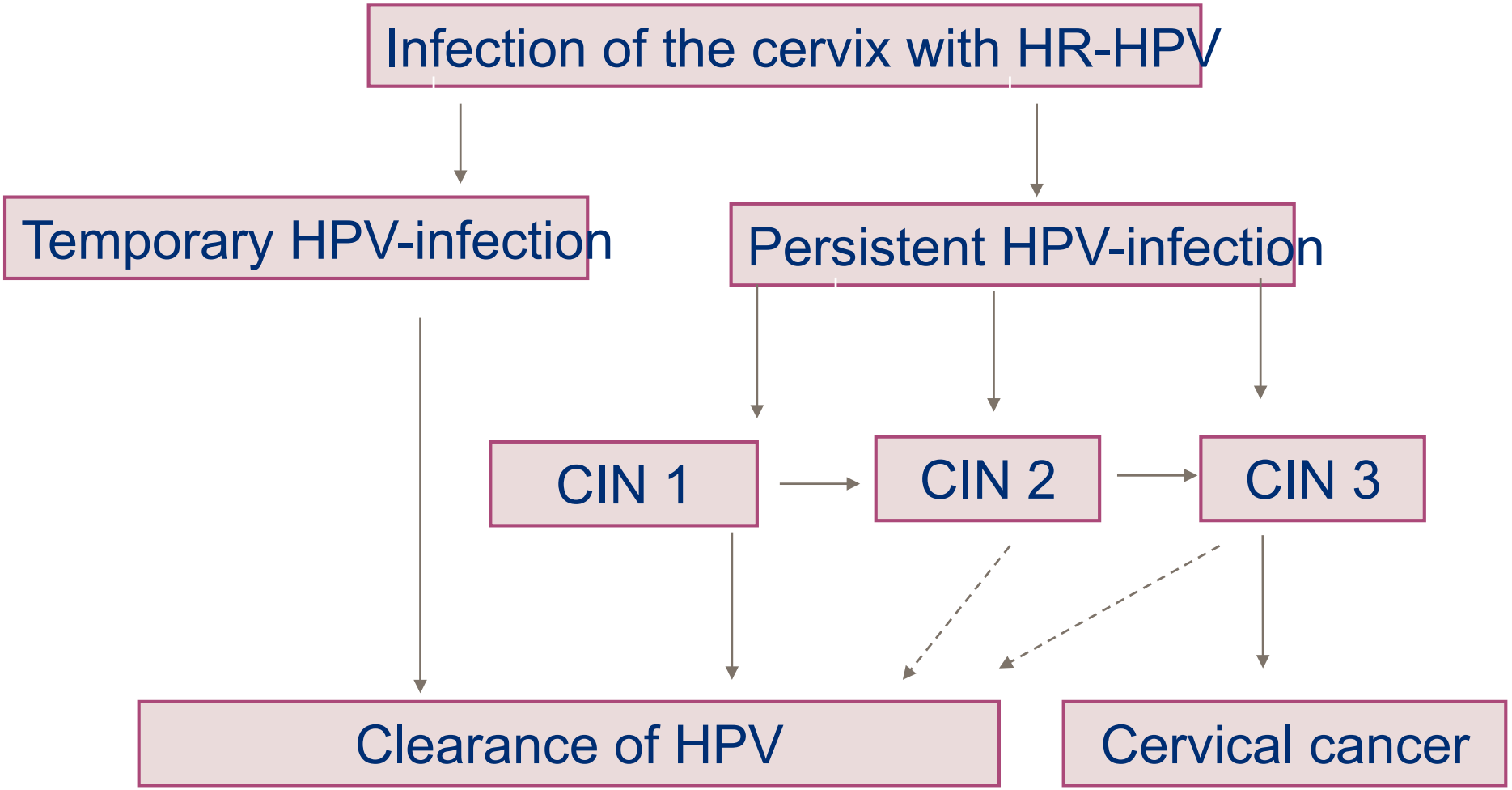


Whichever the region of the world, HPV type 16 and 18 are the main responsible (>70%) for cervical cancer cases (squamous cell carcinoma and adenocarcinoma)

* High-grade lesions include CIN2 and CIN3 lesions

Adapted from: *ICO Information Centre on HPV and Cancer (HPV Information Centre); Human Papillomavirus Related Diseases Report 2014. WORLD Version posted on www.hpvcentre.net in March 17th, 2014 – accessed on http://www.hpvcentre.net/statistics/reports/XWX.pdf. 1.Clifford G et al. Vaccine 2006;24(S3):26-34*;

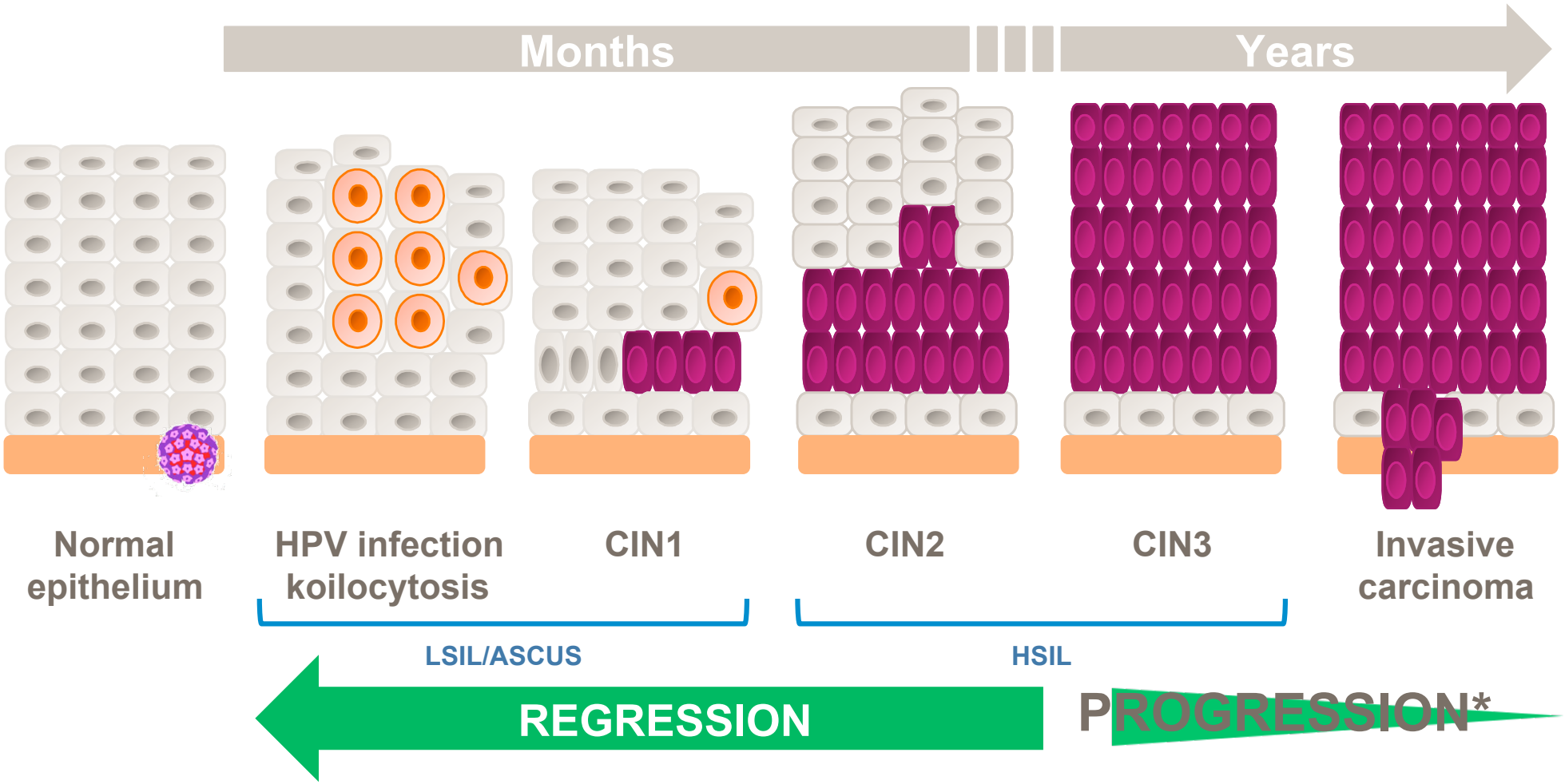
Natural history of cervical cancer



CIN: cervical intraepithelial neoplasia

Adopted from Burgmeijer *et al*. 2007

From HPV infection to cervical cancer: CIN3 is the immediate precursor of invasive cervical cancer



*With increasing probability of viral DNA integration
CIN, cervical intraepithelial neoplasia; LSIL, low-grade squamous intraepithelial lesion; ASCUS, atypical squamous cells of undetermined significance; HSIL, high-grade squamous intraepithelial lesion
Burd. *Clin Microbiol Rev* 2003;16:1–17; Solomon *et al. JAMA* 2002;287:2114–2119

Risks Factors

- Persistent infection with high risk (oncogenic) HPV types is the necessary cause of cervical cancer

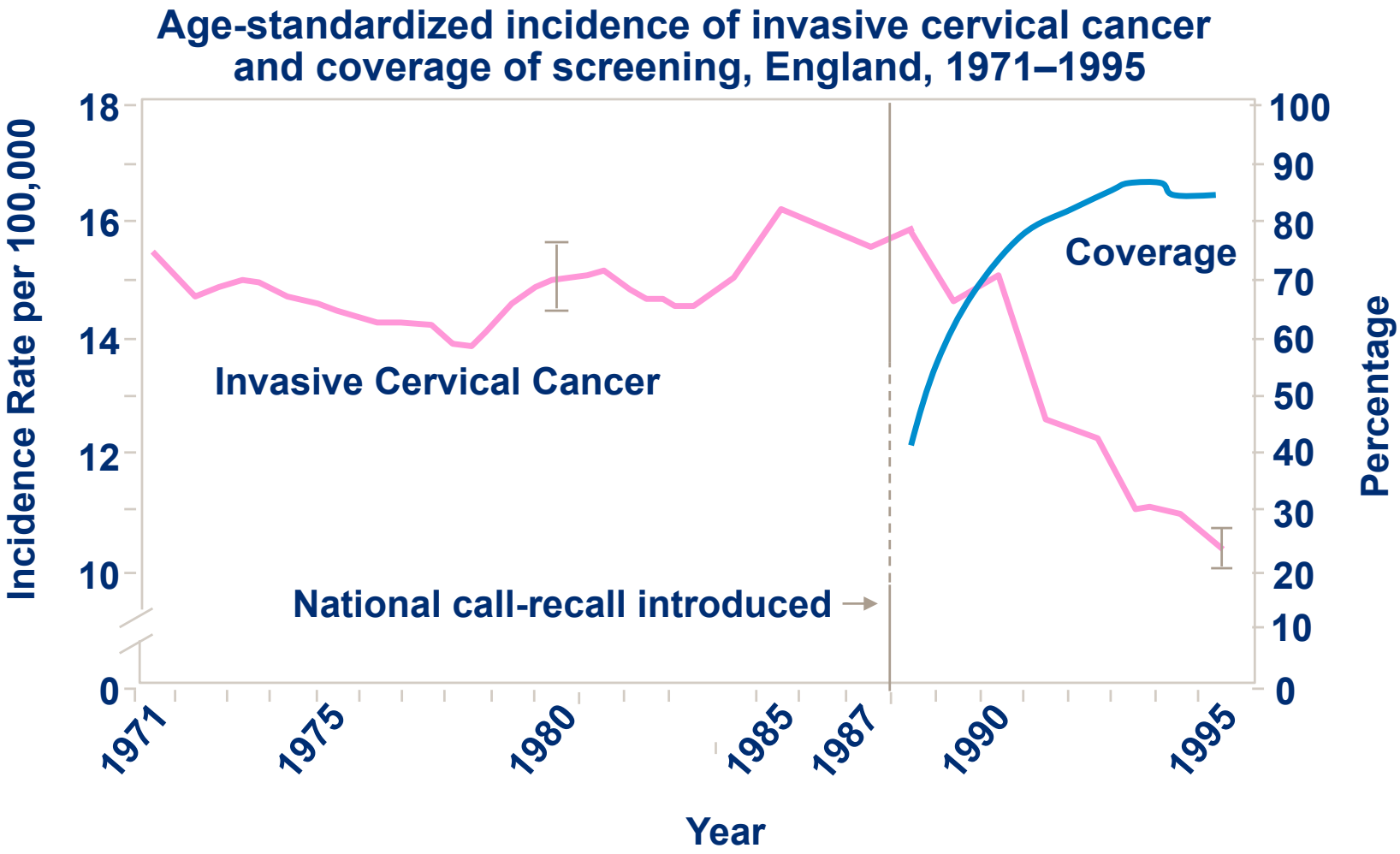
- Factors that could be adding to the risk of persistent HPV infection and cervical cancer:
  - Smoking
  - High parity
  - Long-term use of oral contraceptives
  - Immuno-suppression

HPV and HIV

- Incidence and persistence of HPV infection much higher in HIV infected women; clearance of virus is lower
- Higher HPV viral load in HIV infected women
- Infection with multiple HPV genotypes is more common in HIV positive women
- HIV positive women at greater risk of lower genital tract cytological/ histological abnormalities and (pre) cancers including vulvar and anal cancers
- HIV positive women with invasive cervical cancer almost 5-10 years younger than HIV sero-negative women

Ahdieh et al. J Infect Dis 2001; 184: 682-690.
Denny LA et al. Vaccine 2012; 30S:F168-F174.

Improvements in screening coverage can reduce the incidence of cervical cancer



Adapted from Quinn M, Babb P, Jones J, Allen E. *BMJ.* 1999;318:904–908.

Cervical cancer screening

- Incidence and mortality of cervical cancer (squamous cell carcinoma) has been much reduced in industrialised countries by screening based on cervical cytology (Pap smears) - less impact on adenocarcinoma

- Screening programmes difficult to implement in low-resource settings

- “Opportunistic” screening is not very effective; should be well organised programmes with high coverage. WHO has recently issued screen-and-treat guidelines.

http://www.who.int/reproductivehealth/topics/cancers/guidelines/en/
http://apps.who.int/iris/bitstream/10665/94830/1/9789241548694_eng.pdf

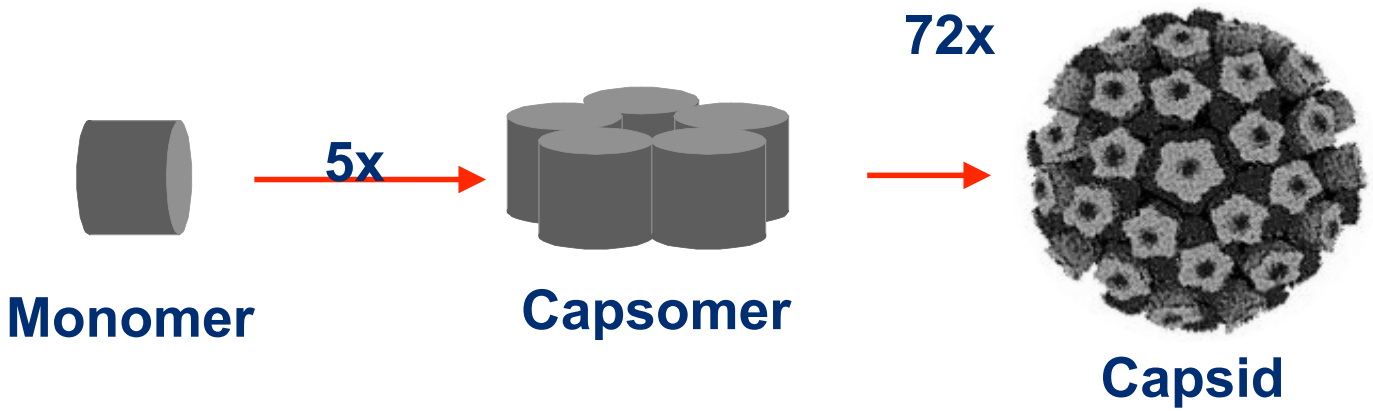
Human Papillomavirus Vaccines

WHO recognizes the importance of cervical cancer and other HPV-related diseases as global public health problems and recommends that routine HPV vaccination should be included in national immunization programmes, provided that: prevention of cervical cancer or other HPV-related diseases, or both, constitutes a public health priority; vaccine introduction is programmatically feasible; sustainable financing can be secured; and the cost effectiveness of vaccination strategies in the country or region is considered

http://www.who.int/wer/2009/wer8415.pdf accessed Nov 2013

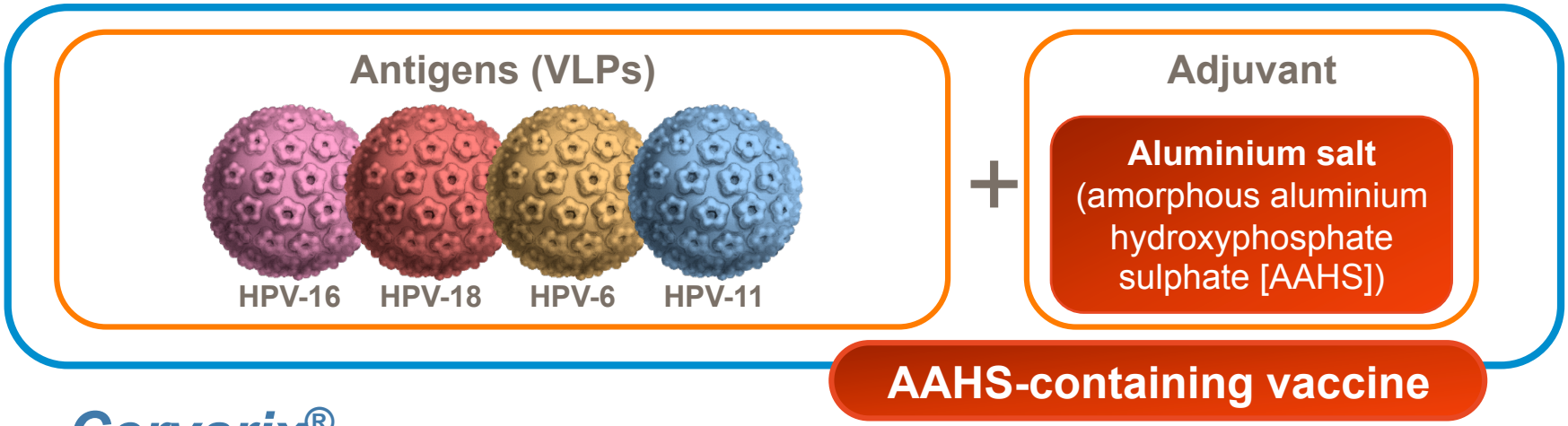
Human Papilloma Virus-like Particles Vaccines

- Prophylactic vaccines are based on recombinant L1 proteins self -assembled into Virus-Like Particles (VLPs).
- L1 is expressed in yeast or baculovirus expression systems, and the protein self-assembles into virus-like-particles.
- VLPs are non-infectious (contain no DNA) and non-oncogenic.

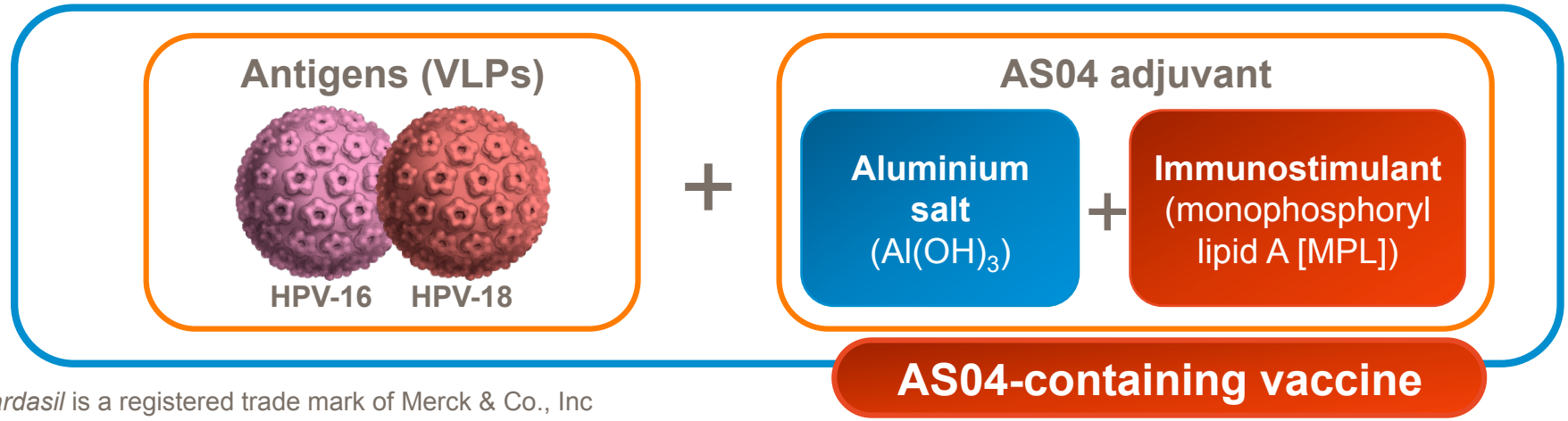


Two HPV vaccines are currently available

Gardasil®



Cervarix®



Gardasil is a registered trade mark of Merck & Co., Inc

Gardasil®. European Summary of Product Characteristics, 2012. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000703/WC500021142.pdf (accessed May 2013); *Cervarix*®. European Summary of Product Characteristics, 2012. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000721/WC500024632.pdf (accessed May 2013). HPV, human papillomavirus; CIN, cervical intraepithelial neoplasia; VLP, virus-like particle.

Characteristics of HPV VLP vaccines

Table 1
Characteristics of HPV VLP vaccines.

	Gardasil®	Cervarix®
Manufacturer	Merck	GlaxoSmithKline
VLP Types	6/11/16/18	16/18
Dose of L1 Protein	20/40/40/20 µg	20/20 µg
Producer Cells	*Saccharomyces cerevisiae* (baker's yeast) expressing L1	*Trichoplusia ni* (Hi 5) insect cell line infected with L1 recombinant baculovirus
Adjuvant	225 µg aluminum hydroxyphosphate sulfate	500 µg aluminum hydroxide, 50 µg 3-O-deacylated-4′-monophosphoryl lipid A
Injection Schedule	0, 2, 6 months	0, 1, 6 months

Gardasil® (Merck & Co., Whitehouse Station, NJ USA).
Cervarix® (GlaxoSmithKline Biologicals, Rixensart, Belgium).
HPV: human papillomavirus; VLP: virus-like particle.

Schiller et al. Vaccine 2012; Suppl 5:F123-38

Efficacy of HPV vaccines

- CIN2+ or CIN3+ and AIS used as endpoints of vaccine efficacy in clinical trials
- Phase II and III clinical trials in females 15-26 years of age
- Immuno-bridging studies compared vaccine immunogenicity in girls aged 9-14 years with females aged 15-26 years
- Both the bivalent and the quadrivalent vaccines show very high efficacy against infection with HPV types 16 and 18
- One of the vaccines is highly efficacious in preventing anogenital warts, a common genital disease which is virtually always caused by infection with HPV types 6 and 11.

http://www.who.int/wer/2009/wer8415.pdf accessed Nov 2013

Efficacy of HPV vaccines in phase III clinical trials

CERVARIX		**Vaccine efficacy (96.1% CI)**
HPV-16/18 CIN2+	ACCORDING TO PROTOCOL	**98.1%** (88.4-100)

Source: Paavonen et al., 2009. Lancet 374: 301-314

GARDASIL		**Vaccine efficacy (95% CI)**
HPV-6/11/ 16/18 HIGH GRADE CERVICAL LESIONS	PER PROTOCOL POPULATION	**98.2%** (93.3-99.8)
HPV-6/11/ 16/18 GENITAL WARTS	PER PROTOCOL POPULATION	**99.0%** (96.2-99.9)

Source: Kjaer et al., 2009. Cancer Prev Res 2: 868-878
Munoz 2010, JNCI 102: 325-339.

Efficacy of HPV vaccines in phase III clinical trials

CERVARIX		**Vaccine efficacy (96.1% CI)**
CIN3+ irrespective of HPV DNA	TOTAL VACCINATED COHORT NAÏVE	**93.2% (78.9–98.7)**

Lehtinen et al. 2012 Lancet Oncol 13: 89-99

GARDASIL		**Vaccine efficacy (96.1% CI)**
CIN3 irrespective of HPV DNA	Negative to 14 HR HPV types population	**43.0 % (13.0-63.2)**
Any genital wart	Negative to 14 HPV types population	**82.8% (74.3-88.8)**

Munoz 2010, JNCI 102: 325-339.

Caution should be applied when comparing these results as these are not head to head studies : differences in the incidence and prevalence will depend on study population .

- Irrespective of HPV DNA = this includes all lesions sampled and analysed, irrespective of the HPV type identified in the lesion, plus lesions in which no HPV DNA was detected
- TVC naive cohort = women who received at least one vaccine dose, were evaluable for effi cacy, and at baseline were HPV DNA negative for all 14 HPV types tested for, seronegative for HPV-16 and HPV-18, and had negative cytology
- Negative to 14 HPV types population = subjects who received at least one dose of vaccine and had any follow-up after day 1 and, at enrollment, were seronegative and negative for HPV6, 11, 16, and 18 DNA; were negative for DNA from all 10 non-vaccine HPV types for which polymerase chain reaction (PCR) testing was available (ie, HPV31, 33, 35, 39, 45, 51, 52, 56, 58, and 59); and had a normal Pap test result.

Additional clinical data from phase III clinical trials

Pease review your country label for the indication included in your setting

- **Gardasil has clinical data**
  - Efficacy in males (1)
  - Efficacy against anal HPV-6-11-16-18 infections (2)
  - For reduction in biopsy and definitive therapy procedures (3)
  - For women with evidence of prior infection (but free of current infection) (4)
  - Efficacy against VIN and VAIN (3)
  - Vaccine efficacy in adult women aged 26-45 years (5)
  - Clinical data in HIV population (6)

(1) Goldstone et al; **Vaccine**. 2013 : 20;31(37):3849-55
(2) Palefsky et al. N Engl J Med. 2011 ;365(17):1576-85
(3) Munoz 2010, JNCI 102: 325-339
(4) Haupt et al;, Int J Cancer. 2011 : 1;129(11):2632-42
(5) Castellsagué et al; Br J Cancer. **2011** Jun 28;105(1):28-37
(6) Giacomet V, et al **Vaccine**. 2014 : 32(43):5657-61

Additional clinical data from phase III clinical trials

Pease review your country label for the indication included in your setting

- **Cervarix has clinical data**
  - Efficacy in adult women
  - Reductions in colposcoy referrals and procedure (1)
  - Anal HPV-16/18 infection in Women (2)
  - HPV-6/11 6 month persistent infections (3)
  - HPV-16 related oral infection (4)
  - Clinical data in HIV population (5)
  - Cervarix has no efficacy data for males

(1) Lehtinen et al. 2012 Lancet Oncol 13: 89-99
(2) Kreimer et al. 2011 Lancet Oncol 12: 862-70
(3) Szarewski et al. 2013 J. Infect. Dis 208: 1391-6
(4) Herrero et al. PLOS one 2013 Jul 17;8(7)
(5) Denny et al., Vaccine. 2013 : 19;31(48

HPV vaccines and HIV

Quadrivalent vaccine:

Study in immune-compromised children in the United States aged between 7 and 12 years. Some of these children were on antiretroviral therapy and some were not.

- Good seroconversion rate: more than 96%
- Lower antibody titers: 50% of those measured in HIV-uninfected children

Levin et al. J Acquir Immune Defic Syndr. 2010; 55(2):197-204
Giacomet V, et al Vaccine. 2014 : 32(43):5657-61

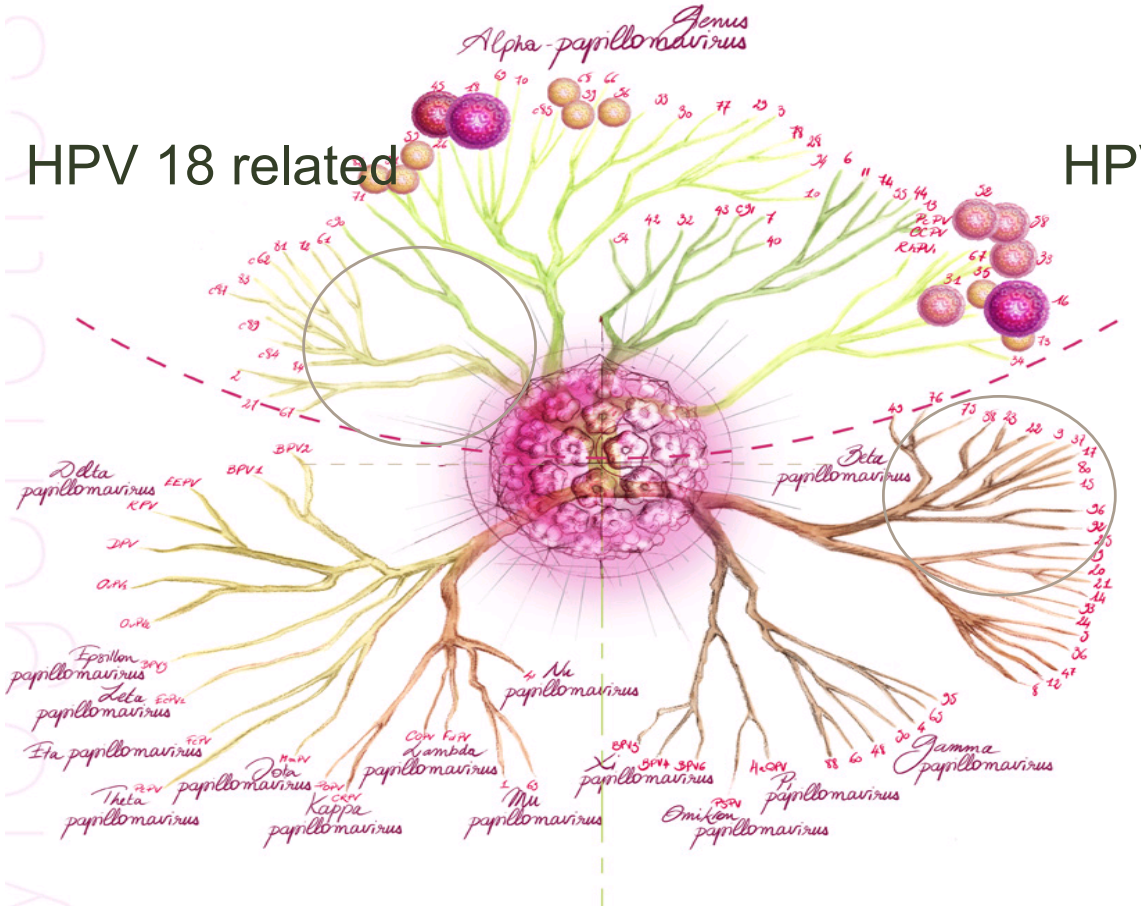
Bivalent vaccine:

A trial on the safety and immunogenicity of the bivalent vaccine in HIV infected females (15-25 age) has recently been completed in South Africa

- Seroconversion rate was 100% for both HIV + /– subjects . All women remained seropostive until the Month 12 timepoint
- No change in CD4+ cell count, HIV viral load and HIV clinical stage

Denny L et al. Vaccine 2013

Cross-protection



Phylogenetically related HPV types (e.g. HPV 18 and 45; HPV 16, 31 and 33) share cross-neutralising epitopes, possible explaining the partial cross-protection.

Cross-protection

Efficacy against CIN2+ – non vaccine types					
End of study TVC naïve populations—Two separate studies—not identical					
Cervarix—Study HPV-008* Event Type	CIN2+				
	n HPV	n Control	VE %	LL	UL
HPV 31	3	28	89.4	65.5	97.9
HPV 33	5	28	82.3	53.4	94.7
HPV 45	0	8	100.0	41.7	100.4
NVT A9 species (HPV 31, 33, 35, 52 or 58)	31	71	56.6	33.0	72.5
NVT A7 species (HPV 39, 45, 59 or 68)	8	28	71.6	36.0	88.8
Gardasil** Event Type	CIN2+				
	n HPV	n Control	VE %	LL	UL
HPV 31	8	27	70.0	32.1	88.2
HPV 33	12	16	24.0	−71.2	67.2
HPV 45	3	2	−51.9	−1717.8	82.6
NVT A9 species (HPV 31, 33, 35, 52 or 58)	44	69	35.4	4.4	56.8
NVT A7 species (HPV 39, 45 or 59)	11	21	47.0	−15.0	76.9

Caution should be applied when comparing these results as these are not head to head studies : differences in the incidence and prevalence will depend on study population .

Szarewski A.; Curr. Oncol Rep. 2012 14(6):559-67.

Immunogenicity of HPV vaccines

- Both vaccines are highly immunogenic and produce high levels of antibodies that are substantially greater than those produced during natural infections. Cross-reactive antibodies have been reported for both vaccines.
- Long-term persistance of antibodies has been demonstrated
  - 8 years for Gardasil (Ferris)
  - 9.4 years for Cervarix (Naud))
  - 35% of women vaccinated with the quadrivalent vaccine lose their antibody titers to HPV18 by 5 years – no breakthrough case seen until now
- A strong anamnestic response was induced after administering a fourth dose after five years for the quadrivalent vaccine and after seven years for the bivalent vaccine (including for the non-vaccine types 31 and 45 with the bivalent vaccine)

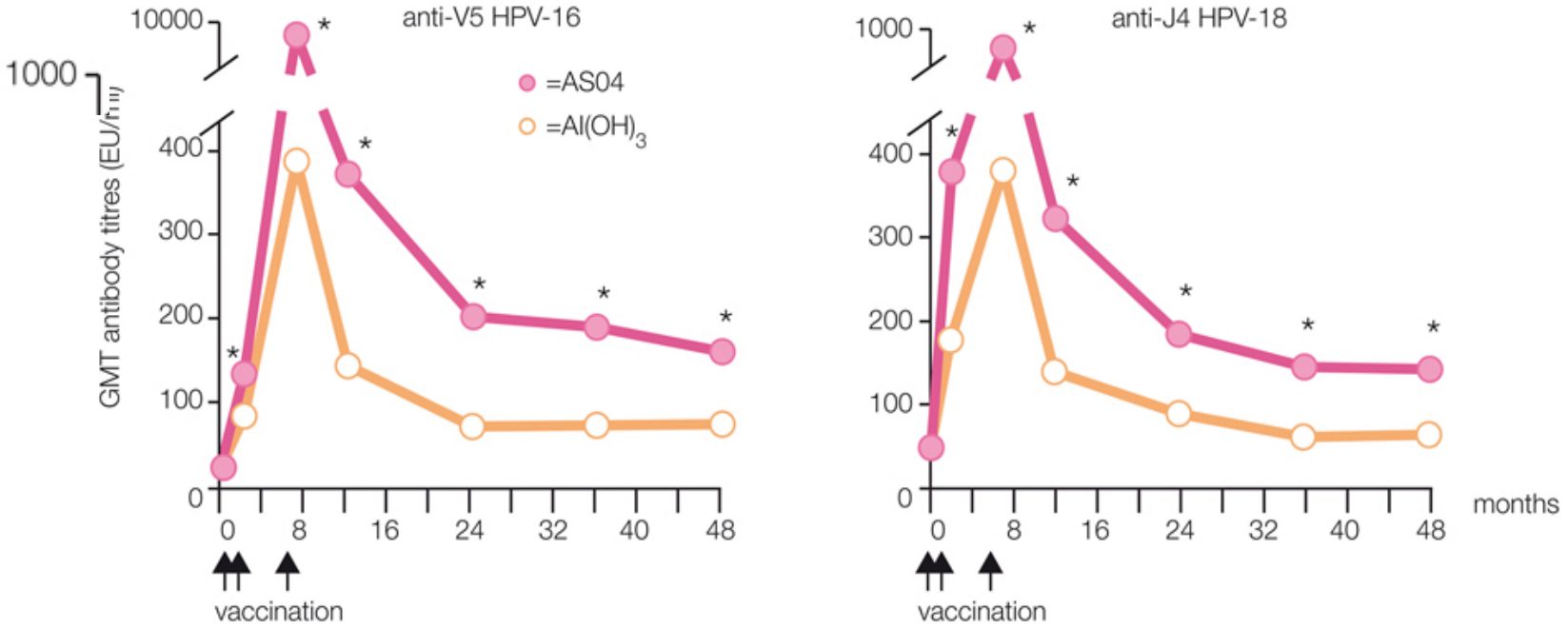
WER (WHO) 2009; 84: 117-132 http://www.who.int/wer/2009/wer8415.pdf
Draper et al, PLOS one 2013
Ferris, Pediatrics 2014
Naud, Hum Vaccin Immunother. 2014 :19;10(8).
Harper, Discovery Medicine, 2010

Impact of AS04 Adjuvant on Antibody levels in Humans

HPV-16/18 L1 VLP vaccine with AS04 or $Al(OH)_3$

V5 epitope is targeted by HPV-16 neutralising antibodies

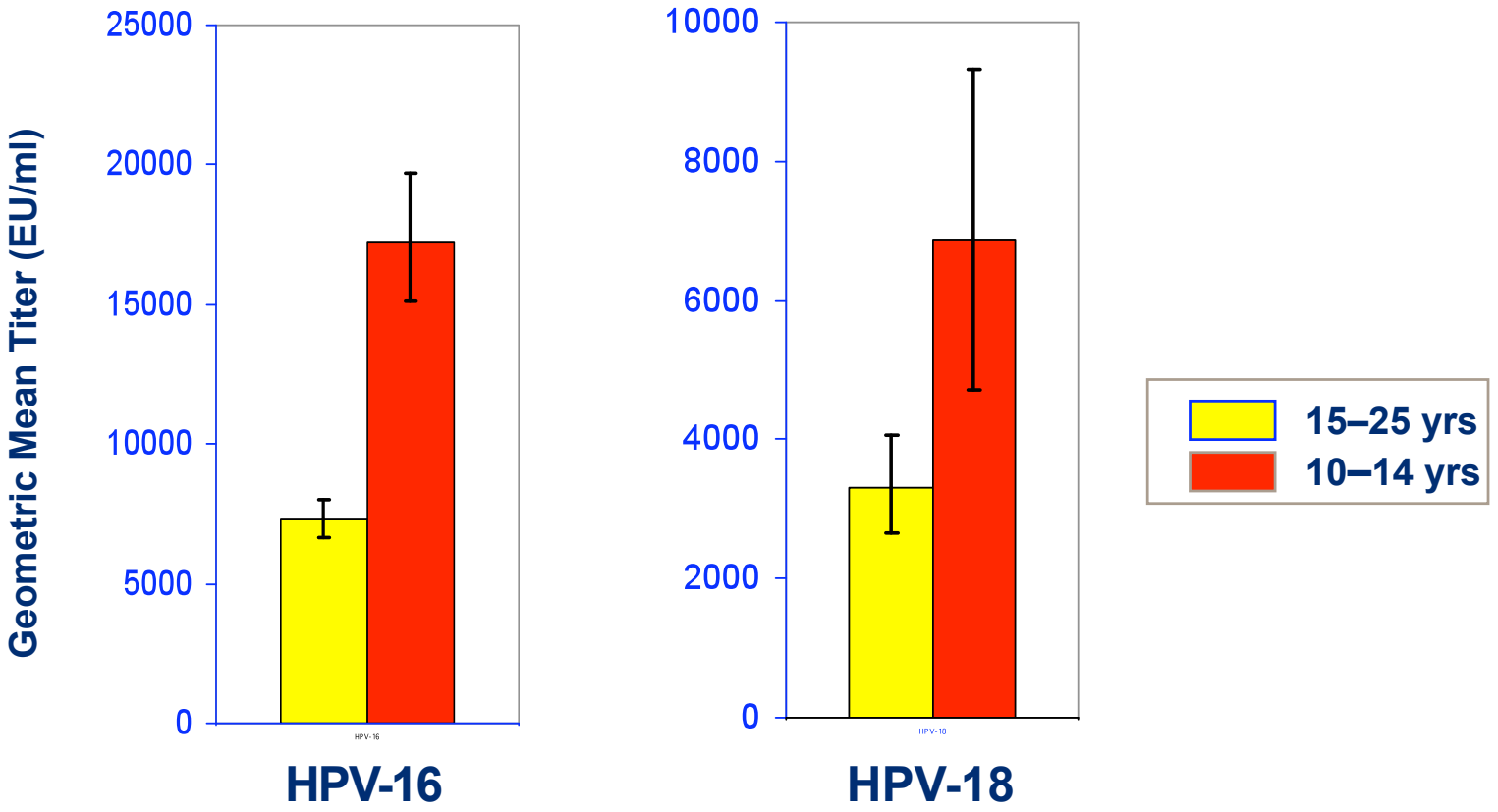
J4 epitope is targeted by HPV-18 neutralising antibodies



* Wilcoxon's non Parametric($p < 0.05$)

Giannini SL, Hanon E, Moris P, *et al. Vaccine* 2006;24: 5937-5949

Bivalent vaccine: Comparison of antibody titers in 10- to 14- and 15- to 25-year-olds (3 dose schedule)



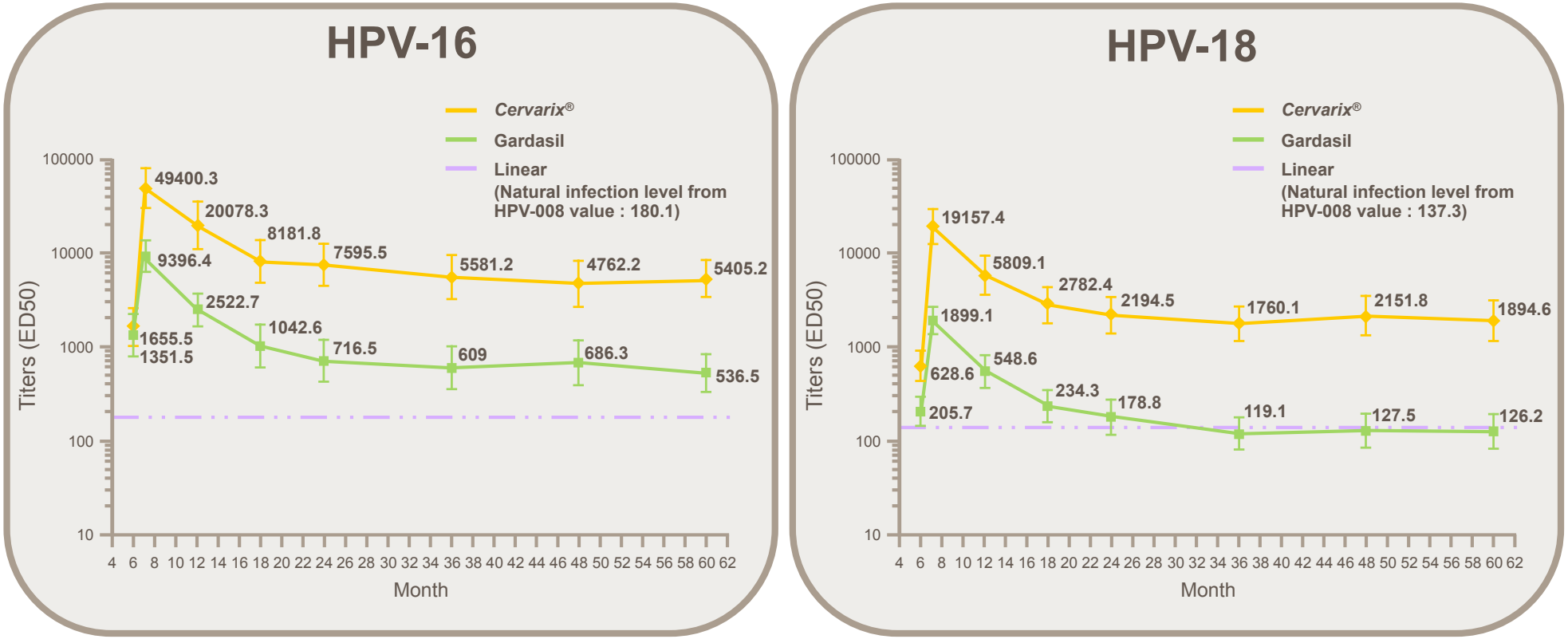
GMTs at month 7 in 10- to 14-year-olds were 2 times higher than 15- to 25 -year-olds.

Adapted from Pedersen et al. J. Adolesc. Health, 2007 Jun;40(6):564-71.

Comparative Trial of the two HPV vaccines

3-dose schedule in women 18-26 years

Serum neutralizing antibodies (PBNA)



For each antigen, positivity was defined as a sample dilution ≥40 ED_{50} (< ED_{50} at baseline). PBNA, pseudovirion-based neutralization assay - Natural infection = 180.1 ED50 and 137.3 ED50 for HPV-16 and -18 nAbs , respectively

This study did not evaluate the relationship between antibody titres and clinical efficacy. A immunological correlate of protection has not been defined. The observed differences in magnitude of immune response might have determinants of duration of protection.

Einstein MH, et al. EUROGIN 2013 abstract SS8-2.

Safety and tolerability of HPV vaccines

- In a comparative trial, Cervarix® had a higher rate of solicited symptoms (mostly injection site reactions) compared to Gardasil®.
- The two vaccines have similar profiles, regardless of age or ethnicity
- Neither vaccine is associated with an increased risk of autoimmune diseases
- Post-marketing surveillance is ongoing for both vaccines published data available for pooled safety data analysis

Szarewski A; Curr Oncol Rep (2012) 14: 559-567

National and Supra-national health authorities continue to reassert the positive benefit/risk profile of HPV vaccines

1. http://www.mhra.gov.uk/home/groups/dsu/documents/publication/con207196.pdf
2. http://www.who.int/vaccine_safety/committee/topics/hpv/130619HPV_VaccineGACVSstatement.pdf
3. http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2013/06/WC500144716.pdf
4. http://www.figo.org/files/figo-corp/Statement%20on%20Safety%20of%20HPV%20vaccination%20-%20FINAL%20-%20AUGUST%202013.pdf

(last accessed Aug 23rd 2013)

Two dose schedule versus three dose schedule

Cervarix:

- Antibody responses obtained with a 2D (month 0, 6) schedule in girls 9-14 years of age are compared to the response to a standard 3-dose schedule in women 15-25 years of age. Non-inferiority of the seroconversion and the immune response has been demonstrated
- Data are available up to 5 years after first vaccination

Gardasil:

- following 2-doses (at 0 and 6 months) antibody responses to HPV 6/11/16/18 were non-inferior at month 7 in 9-13 years old girls, as compared to 3-doses in 16-26 years
- Loss of non-inferiority to some genotypes at 24 to 36 months in girls given 2 doses vs 3 doses (HPV-18 by month 24; HPV-6 by month 36)

Both vaccines have received EMA approval, please check you country label for your indication

http://www.who.int/immunization/sage/meetings/2014/april/1_HPV_Evidence_based_recommendationsWHO_with_Appendices2_3.pdf

Puthanakit T. WSPID, 2013, Cape Town, South Africa; Puthanakit T. EUROGIN, 2013 Florence, Italy;
Romanowski et al., Hum Vac Immunoth 2014;10:5, 1-11; Lazcano-Ponce E et al. Vaccine. 2014 ; 32(6):725-32

Dobson, S.R., et al., JAMA, 2013. 309(17): p. 1793-1802.
Krajden, M., et al., Clin Vaccine Immunol, 2011. 18(3): p. 418-23.
Sankaranarayanan, R., in Eurogin 2013 International Multidisciplinary Congress. 2013: Florence, Italy.
Sankaranarayanan, R. [accessed Nov 2013]; Available from: http://clinicaltrials.gov/show/NCT00923702.

Ongoing research

Bivalent development

- There is also research ongoing to assess immunogenicity in 4-6 year old.

9-valent vaccine development

- This HPV vaccine includes five more HPV types (31, 33, 45, 52, 58) in addition to the four original HPV types in its Gardasil vaccine (6, 11, 16, 18)
- First efficacy and immunogenicity data has been presented at Eurogin 2013
- A 9 valent 2 dose versus 3 dose immuno study is also just started (clinicaltrials.gov)

Programmatic characteristics

Public Health Considerations

- The risk for HPV infection starts from the first sexual encounter and lasts throughout life
- Prophylactic vaccine, not therapeutic → optimal if used before sexual debut. Efficacy has also been demonstrated for women aged above 25 years of age
- Specific features of HPV vaccines: some of these features are of the HPV infection
  - Age for vaccinations
  - Gender issues
  - Sexually transmitted infection
  - Long delay of benefits

Bosch FX, de Sanjose S. *J Natl Cancer Inst Monogr* 2003; 3-13 ; Gravitt PE, Jamshidi R *Inf DiseasesClin North Am* 2005; 19:439-458
SPC Gardasil and SPC Cervarix (EMA)

Public health considerations

Communication:

- Will targeting young adolescent girls for a vaccine to protect from a STI and its deadly consequence be a problem; communicate on HPV vaccine as a cancer prevention vaccine.
- There is evidence showing that HPV vaccination does not impact sexual behaviours in teenagers.

Vaccinate both sexes?

- Modest benefit of male vaccination on herd immunity if coverage of females is sufficiently high (also not cost-effective now).
- Vaccinating males could provide benefits against HPV-related penile cancers in males
- Protection for both genders can be expected for anal; head and neck cancers
- Mathematical models used by Bogaards et al. (2011): Vaccinating the gender with the highest prevalence will reduce the population prevalence most effectively.

Bogaards et al. 2011. PLoS Med 8(12): e1001147.doi: 10.1371/journal.pmed.1001147.

Public health considerations

- Vaccine will impact on cancers caused by HPV types in vaccine
- Cross protection against HPV types not contained in the vaccines has been shown
- Nevertheless, there is still need for a cervical screening programme

    a) no vaccine covers all types and no 100% efficacy irrespective of type and

    b) to prevent disease in those who are not vaccinated

    => simplified screening programme to be developed

Conclusion

Conclusion

- Cervical cancer is caused by a persistent oncogenic HPV infection.
- Efficacious, immunogenic prophylactic HPV vaccines are available.
- They are generally well tolerated and have a clinically acceptable safety profile
- Prophylactic vaccine → optimal if used before sexual debut.
- Interaction between different disciplines and services:
  - Sexual and reproductive health
  - Adolescent health
  - Immunisation programme
  - Cancer control programme
- HPV vaccination could be regarded as the platform for developing and strengthening the adolescent immunisation programme and overall adolescent health services